A framework of immunities for pathogens and hypersensitivities

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Abstract

THfh is to initiate four eradicable immunities. Treg is for four tolerable immunities. TH1/TH1like is immunity for intracellular bacteria/protozoa and type4 hypersensitivity. TH1 includes macrophage1, Tc1, IFNg T helper, and IgG3. TH1like includes macrophage2, suppressive CTL, IFNg/TGFβ T helper, and IgA1. TH2/TH9 is immunity for helminths and type1 hypersensitivity. TH2 includes iEOS, basophil/MCct, IL-4 T helper, and IgE/IgG4. TH9 includes rEOS, basophils/MCt, IL-9 T helper, and IgA2. TH22/TH17 is immunity for extracellular bacteria/fungi and type3 hypersensitivity. TH22 includes neutrophils1, IL-22 T helper, and IgG2. TH17 include neutrophils2, IL-17 T helper, and IgA2. THαβ/TH3 is immunity for viruses and type2 hypersensitivity. THαβ includes NK1, Tc2, IL10 T helper, and IgG1. TH3 includes NK2, suppressive CTL, IL-10/TGFβ T helper, and IgA1.

63 **Background of host immunities**

64

65 There are many discovered host immunological pathways including traditional TH1,
66 TH2, TH3, TH17, TH22, THfh, Treg, TH9, and Tr1(THαβ). These identified
67 pathways are not logically organized. Here, I will propose a detailed picture about the
68 whole context of host immunological pathways. (Figure 1)

69

70 The traditional TH1/TH2 paradigm was proposed by Dr. Mosmann in 1986.(1) TH1
71 was thought the host immunity against viruses and intracellular bacteria. TH2 is the
72 host immunity against multicellular parasites (helminthes). In my PhD thesis, I
73 proposed a new THαβ immunological pathway against viruses that is divided from
74 traditional TH1 immunity.(2) The TH1 immunity is then focusing on intracellular
75 bacteria and protozoa. Then, TH3 immunity and Tr1 immunological pathways were
76 identified later.(3, 4) Recently, additional immune responses are discovered including
77 TH17, TH22, THfh, Treg, and TH1-like immunological pathways.(5-9)

78

79 **Initiatory immune response**

80

81 Follicular helper T cells (THfh) is thought to be the key helper cells for the B cell
82 germinal centers in lymph nodes.(10) THfh cells are characterized by IL-21 producing
83 T cells(11, 12). BCL6 is a key transcription factor for THfh. TGF beta with STAT5
84 signal can constrain the differentiation of the IL-21 producing helper T cells(13, 14).
85 IL-21 production is also related to STAT1and STAT3 activation as well as STAT5
86 activation. Since immunosuppressive prolactin can induce STAT5a to suppress BCL6
87 expression.(15, 16)On the contrary, STAT5b can up-regulate BCL6.(17)STAT5a and
88 STAT5b have distinct target genes in immune responses.(18)The transcription factor

to induce THfh should be STAT5b. BCL6 is key in THfh development.(19-21)Follicular helper T cell can induce B cells to start to produce IgM antibody.(22) Thus, it is the earliest T lymphocytes to begin the adaptive host immunity.(23-25) Different STAT proteins regulate different immunological pathways.(26, 27) If the infection is tend to be eradicable, the following host immunological pathways are generated with other cytokines.

Eradicable immune responses

TH1 immunity is driven by IL-12. It is the host immunity against intracellular bacteria or protozoa. The main effector cells of TH1 immunity are stimulatory macrophages (M1), IFNg secreting cytotoxic CD8 T cells (CD28+ Tc1), IFNg secreting CD4 T cells, and IgG3 producing B cells.(28-31)The key transcription factors for TH1 immunity is STAT4. T-bet also plays a vital role in TH1 immunological pathway. TH1 immunity against self antigen is Type 4 Delayed-type hypersensitivity such as type1 diabetes mellitus.(32, 33)

TH2 immunity is driven by IL-4. TH2 immunity is against extracellular parasites (helminthes). The main effector cells of TH2 immunity are eosinophils (iEOS), basophils/connective tissue mast cells(MCtc, mast cell tryptase & chymase), IL-4/IL-5 secreting CD4 T cells, and IgG4/IgE producing B cells.(34)IgG4 activates eosinophils and IgE activates mast cells such as in acute anaphylaxis, respectively.(35) The function of IgG4-eosinophil is to activate eosinophil mediated cellular immunity against parasites or insects. The function of IgE-mast cell is to expel helminths or insects by physiological mechanism. Activated mast cells by IgE can release histamine which causes bronchoconstriction, vomiting/nausea, rhinorrhea,

115 skin itchiness, stomach acidification, increased local vascular permeability, or
116 increased bowel movement. These actions can all help to expel helminths or insects
117 physiologically. The key transcription factor for TH2 immunity is STAT6. GATA3
118 also plays a vital role in TH2 immunological pathway. TH2 immunity against self
119 antigen is Type1 immediate allergy such as food/drug allergy or urticaria.(36)
120
121 THαβ is distinguished from the traditional TH1 immunity(2). THαβ immunity is
122 against viruses. It was called Tr1 cell by some previous researchers.(4)THαβimmunity
123 is driven by IFNa/b or IL-10. The main effector cells of THαβ immunity are IL-10
124 producing stimulatory NK cells(CD56-CD16+ NK1 cells), IL-10/IL-27 secreting CD4
125 T cells, IL-10 secreting cytotoxic CD8 T cells (CD28+ Tc2), and IgG1 producing B
126 cells.(28, 30, 33, 37, 38)CD27 molecule is important for virus immunity.(39, 40)The
127 key transcription factor for THαβ immunity is STAT1and STAT2.(41)THαβ immunity
128 against self antigen is Type 2 Antibody dependent cytotoxic hypersensitivity such as
129 acute stage of Myasthenia Gravis. It is worth noting that IL-10 is not merely a
130 immunosuppressive cytokine; it can have potent stimulatory effects on NK cells,
131 CTLs, and B cells.(42)
132
133 TH22 is the host innate immunity against extracellular bacteria and fungi(43, 44).
134 TH22 is driven by IL-6 or TNFa(45, 46). The main effector cells for TH22 immunity
135 are PMNs(N1), IL-22 secreting CD4 T cells, complements, pentraxins, and IgG2
136 producing B cells.(6, 47)The key transcription factor for TH22 is STAT3(48). AP1
137 and CEBP are also important. TGF beta can suppress IL-22 to skew to TH17
138 immunity.(49)TH22 against self antigen is Type 3 immune-complex and complement
139 mediated hypersensitivity such as Arthus reaction.(50) It is worth noting that the
140 extracellular or intracellular locations of protozoa or fungi mainly decide the host

141 immunological pathways.

142

143 It is interesting to know that four IgG subtypes fit the four types of acute
144 immunological pathways. Murine IgG antibodies also have four subclasses. There is a
145 correlation between murine and human IgG subtypes: Human IgG1<->Murine IgG2a;
146 Human IgG2<->Murine IgG3; Human IgG3<->Murine IgG2b; Human IgG4<-
147 >Murine IgG1.(51) hIgG1/mIgG2a is against viral antigens; hIgG2/mIgG3 is against
148 bacterial antigen, especially polysaccharides; hIgG3/mIgG2b is against intracellular
149 bacteria; and hIgG4/mIgG1 is related to parasite antigens.(52-55)

150

151 **Regulatory immune responses**

152

153 Treg is the host immune inhibitory mechanism(9). It is driven by IL-2 and TGF beta.
154 The main effector cells for Treg are TGFb producing CD4 T cell and IgA producing B
155 cell. The key transcription factor for Treg pathway is STAT5, especially STAT5a. But,
156 both STAT5a and STAT5b play non-redundant roles in Treg generation.(56) They may
157 act sequentially with STAT5b activation first in THfh signaling. Combined STAT5b
158 and STAT5a signaling induces the generation of Treg. The combination of Treg and
159 the above four immunological pathways is important to shift adaptive immunity to
160 tolerable immunity. During the initial infection, acute stage fierce cytokines can
161 rapidly kill pathogens as well as infected cells or tissues. However, if the pathogen
162 infects a lot of cells in a tissue such as liver, to kill the infected cells will total
163 destroyed the organ.(57) Thus, regulatory T cells STAT5 signal combining
164 TH1/TH2/TH22/THαβ will make CD4 T cells with less fierce cytokines.(56) Then,
165 TH1like/TH9/TH17/TH3 immunological pathways will be generated in more chronic
166 stage. It is worth noting that there are two subtypes of IgA antibodies: IgA1 and IgA2.

167 IgA1 is the dominant IgA antibody in serum, and IgA2 is the dominant IgA in
168 mucosa. TGF beta can induce either IgA1 or IgA2 which seems to be dependent on
169 lymphoid follicle location.(58) In GULTs or Peyer's Patch, IgA2 is the dominant IgA
170 antibody produced in GI mucosa there. In lymph nodes of other body locations, IgA1
171 is the dominant IgA antibody produced there.(59) However, IgA1 is especially related
172 to viral protein antigens and IgA2 is especially related to bacterial antigens such as
173 LPS.(60) The heavy chain locus sequence of B cell antibodies is IgM, IgD, IgG3,
174 IgG1, IgA1, IgG2, IgG4, IgE, and IgA2. First, B cells double express IgM and IgD.
175 We can view IgG3, IgG1, and IgA1 as the first group for cellular immunity. Then,
176 IgG2, IgG4, IgE, and IgA2 can be viewed as the second group for humoral immunity.
177 The gene sequence order is important, and it affects the time sequence of isotype
178 switch. It is also worth noting that IL-13 is also a Treg related cytokine which is pro-
179 fibrogenic and related to TGF beta signaling.(61, 62)
180
181 **Tolerable immune responses**
182
183 TH1-like cells (non-classic TH1) are initiated by TGF beta(STAT5 signaling) and
184 IFNg(STAT4 signaling). TH1-like cells with Foxp3+ regulatory character are
185 identified.(8, 63)There is a close relation to TH1 helper cells and TH1-like cells.(64,
186 65)TH1-like cells are the chronic host immunity of TH1 immune response. Thus, it
187 could be related to chronic inflammation such as long-term tuberculosis infection. The
188 effector cells of TH1-like immunity include suppressive macrophages (M2),
189 suppressive CD8 T cells (CD8 Treg CD28-), IgA1 producing B cells, and IFNg/TGFb
190 producing CD4 T cells.(29, 30, 66, 67)TH1-like immunity induces type4 delayed-type
191 hypersensitivity such as Crohn's disease.(68)
192

193 TH9 cell is driven by IL-4 (STAT6 signaling) combining TGF beta(STAT5
194 signaling).(69-71)Thus, TH9 cell is closely related to TH2 immunological pathway. It
195 is characterized by IL-9 secreting CD4 T cell. TH9 cells are found to be important in
196 chronic allergic condition such as asthma. Thus, TH9 helper cell is the chronic T
197 helper cells related to TH2 immunity. The effector cells of TH9 immunity include
198 regulatory eosinophils(rEOS), basophils/mucosal mast cells (MCt, mast cell tryptase),
199 IL-9 producing CD4 T cells, and IgA2 producing B cells.(72) TH9 immunity induces
200 type1 allergy including asthma.(34, 73-78)
201
202 TH17 cell is driven by IL-6 / IL-1 combining TGF beta(5, 79). Thus, TH17 cell is
203 closely related to TH22 immunological pathway. It is characterized by IL-17 secreting
204 CD4 T cell. TH17 cells are found to be important in chronic immune-complex
205 mediated disease such as rheumatic arthritis. Then, TH17 helper cell is the chronic T
206 helper cell related to TH22 immunity.(80)TGF beta with STAT5 can suppress the
207 acute IL-22 producing cells and enhance the chronic IL-17 producing cells(49, 81).
208 Because of the role of TGF beta in TH17 immunity, regulatory IL-17 producing cells
209 are noted.(82, 83) The effector cells of TH17 immunity include regulatory
210 neutrophils(N2), IL-17 producing CD4 T cells, and IgA2 producing B cells.(60,
211 84)TH17 immunity induces type3 immune-complex hypersensitivity including
212 ulcerative colitis.(85, 86)
213
214 TH3 cells are driven by IL-10 and TGF beta.(87, 88)Thus, TH3 cells are closely
215 related to THαβ immunological pathway. It also produces IL-10 as well as TGF beta.
216 Thus, TH3 helper cell is important to chronic antibody dependent cellular cytotoxic
217 hypersensitivity. TH3 cell is the chronic helper T cells corresponding to THαβ helper
218 cell. The TH3 immune effector cells include IL-13 producing regulatory NK

219 cells(CD56+CD16- NK2 cells), IL-10 and TGF beta secreting CD4 T cells,
220 suppressive CD8 T cells (CD8 Treg CD28-), and IgA1 producing B cells.(30, 38, 89,
221 90) IgA1 is produced in serum and is against viral protein antigens. TH3 immunity
222 induces type2antibody dependent cytotoxic hypersensitivity including chronic stage
223 of SLE.(91, 92)
224
225 **Concluding remarks**
226
227 This summary diagram: 4x2+2 immunological pathways are the whole pictures of
228 host immunological pathways. There are four eradicable immune responses:
229 TH1/TH2/TH22/THαβ which are corresponding to four tolerable immune responses:
230 TH1Like/TH9/TH17/TH3. It will match the four types of hypersensitivity. Then, we
231 can clearly understand the detailed immune response against different pathogens as
232 well as allergy/hypersensitivity.
233
234 **Highlights**
235
236 Recently, many new host immunological pathways other than traditional TH1/TH2
237 diagram were discovered including TH17, TH9, TH22, and Follicular helper T cells.
238
239 Recent studies suggest there is a link between the new immunological pathways and
240 the autoimmunities. However, a detailed framework is still not known.
241
242 Recent studies also suggest different pathogens are related to these newly discovered
243 host immunological pathways. However, we still need a detailed framework to
244 describe the functional classification of host immune responses.

Outstanding questions box

Further studies are needed to verify the accuracy of this new framework of host immunological pathways and their relationship to different pathogens and different types of autoimmune responses.

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Figure legends

Figure 1. The summary diagram of host immunological pathways. In the middle, Tfh side (follicular help T cell) begins the initiatory immunity; on the other hand, Treg side (regulatory T cells) starts the regulatory immunity. Eradicable TH1 and tolerable TH1-like(TH1k) are related in the diagonal line. Eradicable TH2 and tolerable TH9 are related in the diagonal line. Eradicable TH22 and tolerable TH17 are related in the diagonal line. Eradicable THαβ and tolerable TH3 are related in the diagonal line.

Table 1. Summary of host immunological pathways

Immune pathways	Driven cytokine	Transcription factor	Effector cells	CD4 T cells	B cells	Pathogen	Hypersensitivities
Initiatory							
Tfh	IL-21	STAT1, STAT3, STAT5B		IL-21 CD4 T cells	IgM B cells	Acute infection	
Eradicable immunities							
TH1	IL-12	STAT4	Macrophage(M1), CTL(Tc1)	IFNg CD4 T cells	IgG3 B cells	Intracellular bacteria & protozoa	Type 4 DTH
TH2	IL-4	STAT6	Eosinophil(iEOS), basophil, mast cells(MCct)	IL-4 IL-5 CD4 T cells	IgG4/IgE B cells	Helminths & insects	Type 1 allergy
TH22	IL-1	STAT3	Neutrophils(N1)	IL-1, TNFα, IL-22 CD4 T cells	IgG2 B cells	Extracellular bacteria & fungi	Type3 Immune complex
THαβ	IL-10 IFNαβ	STAT1 STAT2	NK cells(NK1), CTL(Tc2)	IL-10 CD4 T cells	IgG1 B cells	viruses	Type 2 ADCC

Immune pathways	Driven cytokine	Transcription factor	Effector cells	CD4 T cells	B cells	Pathogen	Hypersensitivities
Regulatory							
Treg	TGFβ	STAT5A, STAT5B		TGFβ CD4 T cells	IgA B cells	Chronic infection	
Tolerable immunities							
TH1like	IL-12, TGFβ	STAT4, STAT5	Macrophage(M2), CD8 Treg	IFNg/TGFβ CD4 T cells	IgA1 B cells	Intracellular bacteria & protozoa	Type 4 DTH
TH9	IL-4, TGFβ	STAT6, STAT5	Eosinophil(rEOS), basophil, mast cells(MCt)	IL-9 CD4 T cells	IgA2 B cells	Helminths & insects	Type 1 allergy
TH17	IL-6, TGFβ	STAT3, STAT5	Neutrophils(N2)	IL-17 CD4 T cells	IgA2 B cells	Extracellular bacteria & fungi	Type3 immune complex
TH3	IL-10, TGFβ	STAT1 STAT2 STAT5	NK cells(NK2), CD8 Treg	IL-10/TGFβ CD4 T cells	IgA1 B cells	viruses	Type 2 ADCC